Notice of Allowability	Application No.	Applicant(s)	
	10/601,324	CRONIN ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendments filed 04 September 2007*.

2. ☒ The allowed claim(s) is/are *1,2,4,9,10,12,15,26,27,30-32 and 37-39*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☒ Other *See Continuation Sheet*.

Continuation of Attachment(s) 9. Other: Matthews Probability Calculator Data.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Ms. Lekha Gopalakrishnan on 13 September 2007.

The application has been amended as follows:

In the claims:

- Rewrite claim 1: A composition comprising a protein-ligand complex in crystalline form wherein the protein of the complex consists of SEQ ID NO: 3, wherein said protein ~~forms a~~ is in complex with an ATP-binding site ligand, and wherein the protein crystal has a crystal lattice in a $P3_221$ space group and unit cell dimensions, ± 5% of a=72.12 Å, b=72.12 Å and c=241.62 Å.

- Rewrite claim 2: A composition according to claim 1 wherein ~~the protein crystal unit cell comprises two protein complexes~~ there are two molecules of the protein-ligand complex per asymmetric unit of the crystal.

- Rewrite claim 9: A method for forming a crystal of a protein-ligand complex comprising: forming a crystallization volume comprising a precipitant solution and a protein-ligand complex, wherein the protein of the complex consists of SEQ ID NO:3 and is in complex with an ATP-binding site ligand, storing the crystallization volume under conditions suitable for crystal formation of the protein-ligand complex such that a crystal of the protein-ligand complex is formed, wherein the

crystal has a crystal lattice in a $P3_221$ space group and unit cell dimensions, ± 5% of a=72.12 Å, b=72.12 Å and c=241.62 Å.

- Rewrite claim 10: The method according to claim 9 wherein ~~the protein crystal unit cell comprises two protein complexes~~ there are two molecules of the protein-ligand complex per asymmetric unit of the crystal.

- Amend Claim 15: In line 2, insert - - - ligand - - - after "protein".

- Rewrite claim 27: A method according to claim 26 wherein ~~the protein crystal unit cell comprises two protein complexes~~ there are two molecules of the protein-ligand complex per asymmetric unit of the crystal.

- Amend claim 31 to depend from claim 30.

- Amend claim 32 to depend from claim 31.

- Add new claim 39: A non-crystalline protein comprising SEQ ID NO: 3.

- Cancel claims 17 and 33-36.

Formal Matters

2. Previously examined claims 26, 27 and 30-33 were inadvertently withdrawn by Applicants in the amendments filed 04 September 2007. Claims 26, 30-31 should have the status identifier "(Previously Presented)" and claims 27, 31 and 32 "(Currently Amended)".

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: The claims are drawn to crystals of the kinsae domain of the Ephrin receptor A2 (EPHA2) which is bound to an ATP-binding site ligand. SEQ ID No: 3 is used to make said crystal EHPA2 crystal, wherein said sequence has a non-naturally occurring his-tag and linker region and thus the protein is novel in it's non-crystalline form. The crystal forms in space group $P3_221$ with unit cell parameters of ± 5% of a=72.12 Å, b=72.12 Å and c=241.62 Å. Given that the amino acid sequence of SEQ ID No: 3 calculates to a MW of approximately 37 kDa, and given the knowledge in the art of how to calculate how many molecules per asymmetric unit and the solvent content which is derived from the Matthew's Coefficient calculations (e.g.Vm/(MW*Z*X) wherein Vm = volume of the unit cell, MW is molecular weight of the protein, Z= # of symmetry operators in the space group and X is the unknown and what is to be solved for, which is the number of molecules per asymmetric unit. Thus, the calculations give rise to the only plausible answer of two molecules per asymmetric unit and a solvent content of approximately 55% (see attached Matthews Coefficient Calculations based upon 1, 2, 3 and 4

molecules per asymmetric unit). Thus, this has been incorporated into the claim limitations of claims 2, 10 and 27 and is supported in the specification on p. 25, paragraph 110. In addition, the limitations that the protein-complex is SEQ ID No: 3 complexed to an ATP-binding site ligand is seen as enabled because given the exact protein sequence and space group and unit cell parameters, the variables for which one skilled in the art would have to screen for is simplified to one, e.g. the ATP-binding site ligand which is reasonable and would not necessitate any under experimentation. Given that crystallizing any proteins can be extremely unpredictable, the protein claimed in the instant claims have been described and enabled, because of the noted considerable detail of precise protein sequence and space group and unit cell parameters. Finally, the recited genus of ATP-binding site ligands is described as AMP-PNP is deemed representative of the many different ligands which would fit into this binding site either by co-crystallization or by replacement of AMP-PNP through simple soaking of the ligand with the formed crystals. Thus, the claims drawn to the protein crystals and methods of making are novel and non-obvious over the prior art. In addition, the proteins consisting of or comprising SEQ ID No: 3 and those consisting of SEQ ID No: 1 are not found in the prior art. **The allowed claims are: 1, 2, 4, 9, 10, 12, 15, 26, 27, 30-32 and 37-39**.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes whose telephone number is 571-272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
13 September 2007

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

Matthews Probability Calculator

35796

Calculation of Matthews Probabilities and Solvent Content submitted on Wed Sep 12 2007 at 05:07:59 from 151.207.244.4

Unit cell dimensions in A, deg(o) and cubic A :

a	b	c	alpha	beta	gamma	volume
72.1200	72.1200	241.6000	90.000	90.000	90.000	1256632.9

Space group P 32 2 1 , space group number 154, Laue class -3m1 , z= 6

System as decoded from unit cell dimensions : tetragonal
not consistent with space group P 32 2 1 : trigonal

Found 4 possible solutions :

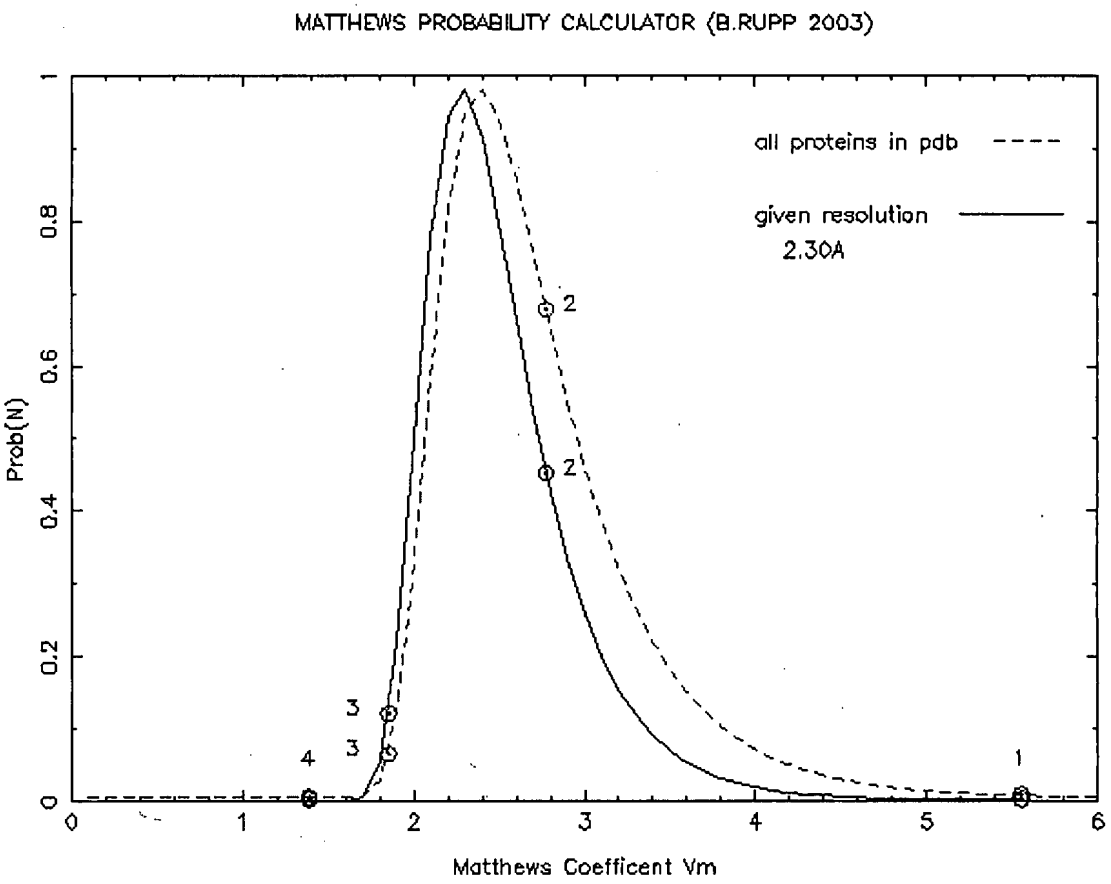
Vm of protein (Matthews coeff.) is 5.55 A**3/Dalton
Estimated solvent content is 77.84 %
Estimated asymmetric unit contents 2816 atoms, 347 residues, 37 kDa
Estimated cell contents 113214 electrons (F000) from protein
366797 electrons from bulk solvent (based on .375 e/A**3)

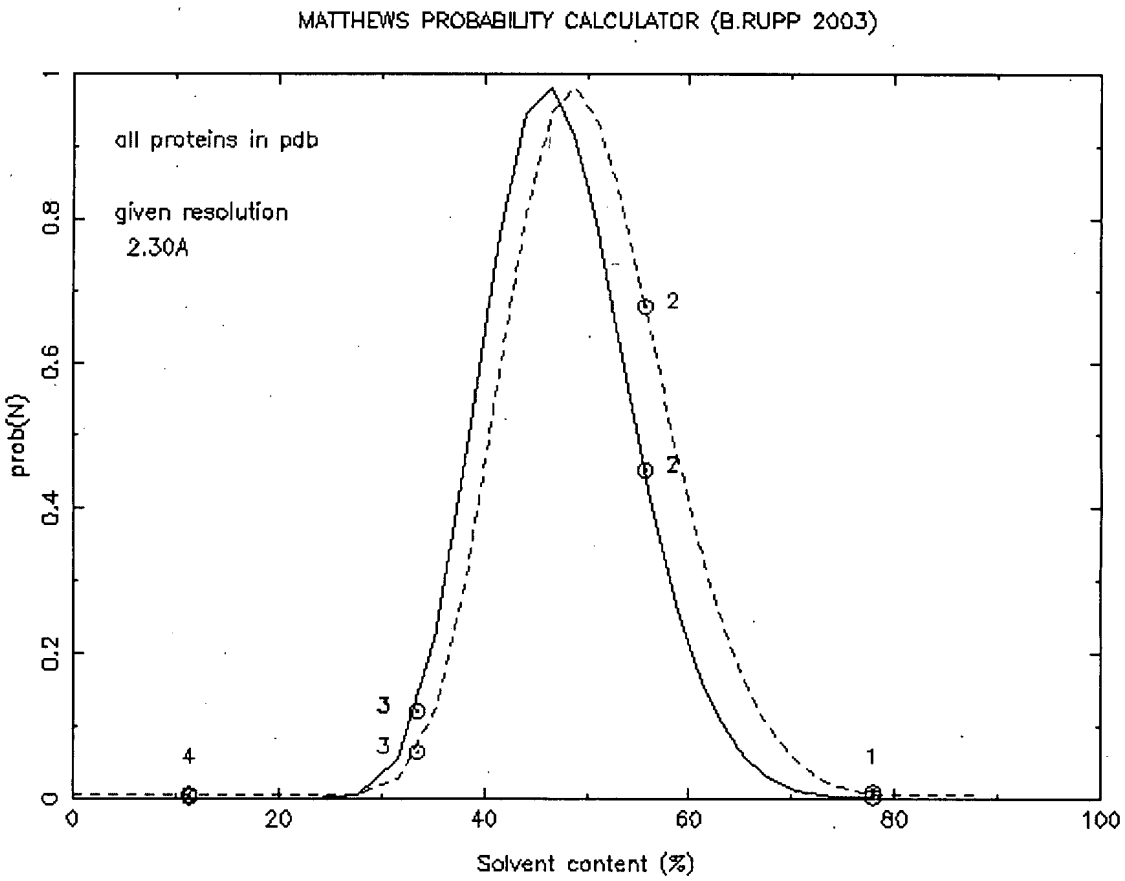
Vm of protein (Matthews coeff.) is 2.77 A**3/Dalton
Estimated solvent content is 55.67 %
Estimated asymmetric unit contents 5632 atoms, 694 residues, 75 kDa
Estimated cell contents 226428 electrons (F000) from protein
262357 electrons from bulk solvent (based on .375 e/A**3)

Vm of protein (Matthews coeff.) is 1.85 A**3/Dalton
Estimated solvent content is 33.51 %
Estimated asymmetric unit contents 8448 atoms, 1041 residues, 113 kDa
Estimated cell contents 339642 electrons (F000) from protein
157917 electrons from bulk solvent (based on .375 e/A**3)

Vm of protein (Matthews coeff.) is 1.39 A**3/Dalton
Estimated solvent content is 11.35 %
Estimated asymmetric unit contents 11265 atoms, 1388 residues, 150 kDa
Estimated cell contents 452856 electrons (F000) from protein
53477 electrons from bulk solvent (based on .375 e/A**3)

N(mol)	Prob(N) for resolution	Prob(N) overall	Vm A**3/Da	Vs % solvent	Mw Da
1	0.00	0.01	5.55	77.84	37738.00
2	0.79	0.90	2.77	55.67	75476.00
3	0.21	0.08	1.85	33.51	113214.00
4	0.00	0.01	1.39	11.35	150952.00


MATTHEWS PROBABILITY CALCULATOR (B.RUPP 2003)
all proteins in pdb
given resolution
2.30A
Prob(N)
Matthews Coefficent Vm
0
0.2
0.4
0.6
0.8
1
2
3
4
5
6
2
2
3
3
4
1


MATTHEWS PROBABILITY CALCULATOR (B.RUPP 2003)
all proteins in pdb
given resolution
2.30A
prob(N)
Solvent content (%)
0
0.2
0.4
0.6
0.8
1
0
20
40
60
80
100
4
3
3
2
2
1